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L1          4125 SEA FILE=CAPLUS OMEPRAZOLE
L2             2 SEA FILE=CAPLUS L1 AND ALKYLAMMON?


=> d l2 1-2 ibib abs hit

L2   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:719472  CAPLUS
DOCUMENT NUMBER:          139:235513
TITLE:                    Alkylammonium salts of omeprazole
                          and esomeprazole
INVENTOR(S):              Dahlstroem, Mikael
PATENT ASSIGNEE(S):       Astrazeneca AB, Swed.
SOURCE:                   PCT Int. Appl., 27 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
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     WO 2003074514         A1    20030912    WO 2003-SE378          20030304
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2474246            AA    20030912    CA 2003-2474246        20030304
     AU 2003208686         A1    20030916    AU 2003-208686         20030304
     EP 1487818            A1    20041222    EP 2003-707279         20030304
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2005521693	T2	20050721	JP 2003-572982		20030304
US 2005182099	A1	20050818	US 2003-506345		20030304
PRIORITY APPLN. INFO.:			US 2002-362187P	P	20020305
			WO 2003-SE378	W	20030304

AB The present invention relates to salts of **omeprazole** and its (S)-enantiomer, esomeprazole. More specifically, the present invention relates to **alkylammonium** salt of the compds., formed by a reaction of **omeprazole** and esomeprazole, resp., and an alkylamine. A process for preparing crystalline salts, a pharmaceutical preparation and a method for treatment of gastric acid related disorders by administering the compound of the invention are also described.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Alkylammonium** salts of **omeprazole** and esomeprazole

AB The present invention relates to salts of **omeprazole** and its (S)-enantiomer, esomeprazole. More specifically, the present invention relates to **alkylammonium** salt of the compds., formed by a reaction of **omeprazole** and esomeprazole, resp., and an alkylamine. A process for preparing crystalline salts, a pharmaceutical preparation and a method for treatment of gastric acid related disorders by administering the compound of the invention are also described.

ST **omeprazole** esomeprazole **alkylammonium** salt prepn gastric acid disorder

IT Drug delivery systems
(preparation of **omeprazole** and esomeprazole **alkylammonium** salts for treatment of gastric acid related disorders)

IT Amines, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **omeprazole** and esomeprazole **alkylammonium** salts for treatment of gastric acid related disorders)

IT Gastric acid
(secretion, disorders related to; preparation of **omeprazole** and esomeprazole **alkylammonium** salts for treatment of gastric acid related disorders)

IT 595555-77-4P 595555-78-5P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of **omeprazole** and esomeprazole **alkylammonium** salts for treatment of gastric acid related disorders)

IT 75-64-9, tert-Butylamine, reactions 73590-58-6, **Omeprazole** 161796-78-7, Esomeprazole sodium
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **omeprazole** and esomeprazole **alkylammonium** salts for treatment of gastric acid related disorders)

IT 119141-88-7P, Esomeprazole
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **omeprazole** and esomeprazole **alkylammonium** salts for treatment of gastric acid related disorders)

L2 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1995:444179 CAPLUS
DOCUMENT NUMBER:	122:214069
TITLE:	Process for the preparation of optically pure crystalline salts of **omeprazole**
INVENTOR(S):	Lindberg, Per Lennart; Von Unge, Sverker
PATENT ASSIGNEE(S):	Astra AB, Swed.
SOURCE:	PCT Int. Appl., 30 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9427988	A1	19941208	WO 1994-SE509	19940527
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
IN 183897	A	20000513	IN 1994-DE562	19940506
TW 389761	B	20000511	TW 1994-83104255	19940511
HR 940307	B1	20010630	HR 1994-940307	19940517
LT 3287	B	19950626	LT 1994-1941	19940518
IL 109684	A1	20020523	IL 1994-109684	19940519
ZA 9403557	A	19950411	ZA 1994-3557	19940523
CA 2337581	AA	19941208	CA 1994-2337581	19940527
AU 9469024	A1	19941220	AU 1994-69024	19940527
AU 676337	B2	19970306		
EP 652872	A1	19950517	EP 1994-917244	19940527
EP 652872	B1	20001108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1110477	A	19951018	CN 1994-190335	19940527
CN 1055469	B	20000816		
JP 07509499	T2	19951019	JP 1994-500553	19940527
JP 07509499	T2	19951019	JP 1995-500553	19940527
JP 3549111	B2	20040804		
HU 71888	A2	19960228	HU 1995-247	19940527
RU 2137766	C1	19990920	RU 1995-105587	19940527
EP 1020460	A2	20000719	EP 2000-108479	19940527
EP 1020460	A3	20031015		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI				
EP 1020461	A2	20000719	EP 2000-108480	19940527
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI				
PL 178994	B1	20000731	PL 1994-307261	19940527
AT 197452	E	20001111	AT 1994-917244	19940527
ES 2099047	T3	20010301	ES 1994-917244	19940527
CZ 287876	B6	20010314	CZ 1995-202	19940527
PT 652872	T	20010430	PT 1994-917244	19940527
CA 2139653	C	20010710	CA 1994-2139653	19940527
SK 282524	B6	20021008	SK 1995-101	19940527
US 5693818	A	19971202	US 1994-256174	19940628
LV 11034	B	19961020	LV 1994-266	19941230
NO 9500263	A	19950124	NO 1995-263	19950124
NO 307378	B1	20000327		
FI 9500377	A	19950127	FI 1995-377	19950127
HK 1008330	A1	20010706	HK 1998-109228	19980717
CN 1259346	A	20000712	CN 1999-118539	19990903
CN 1107503	B	20030507		
GR 3035365	T3	20010531	GR 2001-400191	20010205
JP 2004043493	A2	20040212	JP 2003-317637	20030910
JP 2004043494	A2	20040212	JP 2003-317639	20030910

PRIORITY APPLN. INFO.:

SE 1993-1830	A	19930528
CA 1994-2139653	A3	19940527
EP 1994-917244	A3	19940527
JP 1995-500553	A3	19940527

WO 1994-SE509 W 19940527

OTHER SOURCE(S): MARPAT 122:214069

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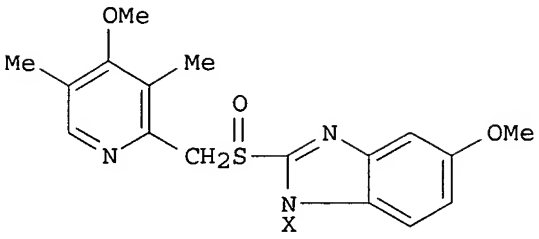

I

AB Optically pure Na+, Mg2+, Li+, K+, Ca2+, and quaternary **alkylammonium** salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ulcer inhibitors are prepared from diastereomeric derivs. (I; X = chiral acyloxymethyls) which are separated by chromatog. or fractional crystallization and dissolved in an alkaline solution of a protic solvent (e.g., alcs., H2O) or with a base (e.g., NaOH) in an aprotic solvent (e.g., DMF, DMSO). Formulations containing the chiral **omeprazole** salts are presented.

TI Process for the preparation of optically pure crystalline salts of **omeprazole**

AB Optically pure Na+, Mg2+, Li+, K+, Ca2+, and quaternary **alkylammonium** salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ulcer inhibitors are prepared from diastereomeric derivs. (I; X = chiral acyloxymethyls) which are separated by chromatog. or fractional crystallization and dissolved in an alkaline solution of a protic solvent (e.g., alcs., H2O) or with a base (e.g., NaOH) in an aprotic solvent (e.g., DMF, DMSO). Formulations containing the chiral **omeprazole** salts are presented.

ST chiral **omeprazole** salt prepn resoln; ulcer inhibitor prepn
chiral **omeprazole**

IT Ulcer inhibitors
(chiral **omeprazole** salts)

IT Resolution
(of chiral **omeprazole** salts)

IT 119141-88-7D, quaternary **alkylammonium** salts 119141-89-8D, quaternary **alkylammonium** salts 161796-80-1 161796-81-2 161796-82-3 161796-83-4 161796-84-5 161796-85-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(claimed compound; process for the preparation of optically pure crystalline salts of **omeprazole**)

IT 67-68-5, Dmso, uses 68-12-2, Dmf, uses 1310-73-2, Sodium hydroxide, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for the preparation of optically pure crystalline salts of **omeprazole**)

IT 119141-88-7P 119141-89-8P 161796-77-6P 161796-78-7P 161796-86-7P 161796-87-8P 161796-88-9P 161796-89-0P 161973-10-0P 161973-11-1P

RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for the preparation of optically pure crystalline salts of **omeprazole**)

IT 107-31-3, Methyl formate 118293-26-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the preparation of optically pure crystalline salts of **omeprazole**)

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FILE 'USPATFULL' ENTERED AT 10:28:18 ON 06 APR 2006
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FILE 'USPAT2' ENTERED AT 10:28:18 ON 06 APR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

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L1 4125 SEA FILE=CAPLUS OMEPRAZOLE
L2 2 SEA FILE=CAPLUS L1 AND ALKYLAMMON?
L3 11 SEA L2

=> d l3 1-11 ibib abs hit

L3 ANSWER 1 OF 11 USPATFULL on STN
ACCESSION NUMBER: 2005:209614 USPATFULL
TITLE: **Alkylammonium** salts of omepazole and esomeprazole
INVENTOR(S): Dahlstrom, Mikael, Molndal, SWEDEN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2005182099	A1	20050818	
APPLICATION INFO.:	US 2003-506345	A1	20030304	(10)
	WO 2003-SE378		20030304	

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-362187P	20020305 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WHITE & CASE LLP, PATENT DEPARTMENT, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036, US
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 599
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to new salts of **omeprazole** and esomeprazole respectively, i.e. salts of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and the (S)-enantiomer thereof. More specifically, the present invention relates to **alkylammonium** salt of the compounds, formed by a reaction of **omeprazole** and esomeprazole respectively and an alkylamine with formula NR?1#191R?2#191R?3#191 wherein R?1#191 is a linear, branched or cyclic C?1#191-C?12#191-alkyl group, R?2#191 and R?3#191 are hydrogen. The present invention also relates to a process for preparing crystalline salts, a pharmaceutical preparation and a method for treatment of gastric related disorders by administering the compound of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Alkylammonium** salts of omepazole and esomeprazole

AB The present invention relates to new salts of **omeprazole** and esomeprazole respectively, i.e. salts of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and the (S)-enantiomer thereof. More specifically, the present invention relates to **alkylammonium** salt of the compounds, formed by a reaction of **omeprazole** and esomeprazole respectively and an alkylamine with formula NR?1#191R?2#191R?3#191 wherein R?1#191 is a linear, branched or cyclic C?1#191-C?12#191-alkyl group, R?2#191 and R?3#191 are hydrogen. The present invention also relates to a process for preparing crystalline salts, a pharmaceutical preparation and a method for treatment of gastric related disorders by administering the compound of the invention.

SUMM The present invention relates to novel salts of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or salts of the single enantiomers thereof in a pure and isolated form. Specifically, it relates to **alkylammonium** salts of the compounds, more specifically primary **alkylammonium** salts of the compounds. The present invention also relates to processes for preparing certain **alkylammonium** salts of **omeprazole** and esomeprazole in a pure and isolated form and pharmaceutical compositions containing them.

SUMM The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name **omeprazole**, and therapeutically acceptable salts thereof, are described in EP 0 005 129.

SUMM **Omeprazole** is a sulfoxide and a chiral compound, wherein the sulphur atom being the stereogenic center. Thus, **omeprazole** is a racemic mixture of its two single enantiomers, the R- and S-enantiomer of **omeprazole**, herein referred to as R-**omeprazole** and S-**omeprazole**, the latter have the generic name esomeprazole. The absolute configuration of the enantiomers of **omeprazole** has been determined by an X-ray study of an N-alkylated derivate of the R-enantiomer.

SUMM **Omeprazole** and esomeprazole are proton pump inhibitors, and are useful as antiulcer agents. In a more general sense, **omeprazole** and esomeprazole may be used for prevention and treatment of gastric acid related diseases in mammals and especially in man.

SUMM Specific alkaline salts of **omeprazole** are disclosed in EP 0 124 495. Herein, quaternary ammonium salts and guanidine salts of **omeprazole** are disclosed. Document WO 97/41114 discloses processes for preparing magnesium salt of benzimidazoles, including magnesium salt of **omeprazole**. However, no salts of **omeprazole** prepared from primary amines are mentioned in these documents.

SUMM Certain salts of the single enantiomers of **omeprazole** and their preparation are disclosed in WO 94/27988, for instance, quaternary ammonium salts of esomeprazole are mentioned. However, no salts employing primary, secondary or tertiary amines are disclosed or suggested. The described salts of esomeprazole have improved pharmacokinetic and metabolic properties, which will give an improved therapeutic profile such as a lower degree of interindividual variation. WO 96/02535 and WO 98/54171 disclose preferred processes for preparing esomeprazole and salts thereof.

DRWD FIG. 1 is an X-ray powder diffractogram of the tert-butylammoniumsalt of **omeprazole**.

DETD The present invention refers to new **alkylammoniumsalts** having the following formula (I) including compounds Ia, Ib and Ic: ##STR1##

Formula Ia: **alkylammoniumsalts** of racemic **omeprazole**

Formula Ib: **alkylammoniumsalts** of the (S)-enantiomer of **omeprazole**

Formula Ic: **alkylammoniumsalts** of the (R)-enantiomer of **omeprazole** wherein R.sub.1 is selected from linear, branched or cyclic C.sub.1-C.sub.12-alkyl group; R.sub.2 is hydrogen; a linear, branched or cyclic C.sub.1-C.sub.12-alkyl group; and, R.sub.3 is hydrogen; a linear, branched or cyclic C.sub.1-C.sub.12-alkyl group.

DETD Further, the compound of the invention is **alkylammoniumsalt** of Formula Ia and Ib wherein the substituents R.sub.1, R.sub.2 and R.sub.3 are defined as follows: R.sub.1 is a linear or branched C.sub.1-C.sub.6 alkyl group; R.sub.2 is hydrogen; a linear or branched C.sub.1-C.sub.6 alkyl group; R.sub.3 is hydrogen; a linear or branched C.sub.1-C.sub.6 alkyl group.

DETD In a further aspect, the present invention provides processes for the preparation of **alkylammonium** salts of **omeprazole** and of esomeprazole. It has surprisingly been found that **alkylammonium** salts of **omeprazole** and **alkylammonium** salts of the R- and S-enantiomers thereof may be obtained in a well-defined crystalline state. More specifically, the compounds tert-butylammoniumsalt of **omeprazole** and tert-butylammoniumsalt of esomeprazole according to the present invention are characterized by being highly crystalline with a well-defined structure.

DETD Another embodiment of the invention is the tert-butylammonium salt of **omeprazole**. This compound of the invention is characterized in providing an X-ray powder diffraction pattern, as in FIG. 1, exhibiting substantially the following d-values and intensities:

d-value (Å)	Relative intensity
14.5	vs
10.4	vs
10.3	vs
7.2	vs
6.8	m
6.2	m
6.0	m
5.8	vs
5.5	s
5.1	vs
5.1	s
4.93	s
4.81	s
4.60	s
4.42	s
4.37	s
4.37	s
4.34	vs
4.02	m
3.86	vs
3.70	s
3.65	s
3.59	m

3.11	s
3.08	s
3.02	m
2.92	m
2.60	m

DETD The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of tert-butylammonium salt of esomeprazole and **omeprazole**, respectively. The relative intensities are less reliable and instead of numerical values, the following definitions are used;

% relative Intensity*	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)

*the relative intensities are derived from the diffractograms measured with variable slits. The XRPD distance values may vary in the range of ±2 on the last decimal place.

DETD X-ray powder diffraction (XRPD) analysis was performed on samples of tert-butylammonium salt of **omeprazole** and on samples of tert-butylammoniumsalt of esomeprazole, according to standard methods, for example, those described in Giacovazzo, C. et al. (1995), Fundamentals of Crystallography, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-ray Diffraction Procedures, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer.

DETD In a further aspect, the present invention provides processes for the preparation of **alkylammoniumsalts** of **omeprazole** and of esomeprazole. Suitable processes for the salt formation are temperature induced crystallisation, fast crystallisation at elevated temperature, slow crystallisation at room temperature, thermal recrystallisation, and crystallisation by evaporation.

DETD In a further aspect, the present invention provides processes for the preparation of **alkylammonium** salts of **omeprazole** and of esomeprazole, which comprises the following steps: **omeprazole** or esomeprazole is either dissolved or formed in situ in a suitable solvent, such as acetonitril or tert-butyl methyl ether. The alkylamine is added during stirring. A precipitate of the salt compound is formed and the precipitate is separated by filtration. The obtained compound is washed with a solvent and the obtained crystals are dried.

DETD Still a further aspect of the invention is that the novel compounds may be of interest as intermediates in the synthesis of other compounds such as magnesium salts of **omeprazole** and of esomeprazole, which are the pharmaceutically active components in products with the tradenames Losec® MUPS® and Nexium®. During the synthesis of the active component for Nexium® i.e. the magnesium salt of esomeprazole, a titanium catalyst may be used in the oxidation step prior to the salt formation steps. The synthesis usually proceeds with the formation of monovalent salt of esomeprazole by adding a monovalent hydroxide or alkoxide. This monovalent salt of esomeprazole, such as sodium or potassium salts, is thereafter converted to the magnesium salt. Insoluble inorganic titanium salts, such as titanium oxid, are being formed when strong bases such as sodium or potassium alkoxides are being added to a solution of titanium catalysts. Using an alkylamine as a salt forming agent rather than using a sodium- or potassium-containing base avoids the risk of inorganic titanium salts being co-precipitated

with the desired salt. Even, if the titanium-catalyst may react with the alkylamine, a soluble complex of the alkylamine and titanium may be formed, which may stay in the solution while filtering off the desired **alkylammonium** salt of the benzimidazole compound.

DETD As synthetic intermediate salts, **alkylammonium** salts of **omeprazole** and esomeprazole obtainable from easily removable amines are desired. In previous known processes for producing salts of esomeprazole (described in WO 96/02535 and WO 98/54171) an exchange of the metal ion is performed. For example, in the process for producing magnesium salt of esomeprazole, an intermediate salt consisting of the potassium salt of esomeprazole is formed which may result in residues of potassium ions as impurity ions in the desired, magnesium salt of esomeprazole.

DETD By preparing and using the **alkylammoniumsalts** as intermediate salts, undesired components are avoided in the final product, i.e. the magnesium salt, as alkylamine is being released during the addition of a magnesium source. Liberated alkylamine can then be removed either by drying the magnesium salt in vacuum or by washing the magnesium salt.

DETD The compounds of the invention are surprisingly easily soluble in water. This property is of great advantage, for instance when an i.v.-formulation should be prepared. Solutions containing the dissolved and ionised **alkylammonium** salt of **omeprazole** or **alkylammonium** salt of esomeprazole have a lower pH than corresponding solutions made from the previously known alkali-salts of **omeprazole** and of esomeprazole. A less basic solution is advantageous for i.v. administration.

DETD The examplified tert-butylammonium salts of **omeprazole** and esomeprazole, respectively, are in crystalline forms. They exhibit advantageous properties, such as convenient handling as well as chemical and solid-state stability. The products obtained according to the present invention are well-defined crystalline products. Such crystalline products give an easily processability during the manufacture of suitable dosage forms. A crystalline product is easy to handle during milling, filtering and tableting. The procedures have high reproducibility. Also, the stability is improved when a well-defined crystalline form of the compound is obtained. These properties are of great value considering dosage forms such as e.g. tablets.

DETD Any suitable route of administration may be employed for providing the patient with an effective dosage of the alkyl ammonium salt of **omeprazole** or esomeprazole, according to the invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

DETD **Omeprazole** (1.0 g, 2.9 mmol) was dissolved in tert-butyl methyl ether (10 ml) at 60-70° C. Tert-butylamine (0.60 g, 8.1 mmol) was added and the mixture was then cooled to room temperature whereupon the product crystallised. The formed precipitate was filtered off and washed with in tert-butyl methyl ether. The title compound was obtained as a white solid.

CLM What is claimed is:

1. An NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole**, wherein: R.sub.1 is a linear or branched C.sub.1-C.sub.12-alkyl group, or a cyclic C.sub.3-C.sub.12-alkyl group, wherein the linear or branched C.sub.1-C.sub.12 alkyl group is optionally substituted or interrupted with a substituent selected from the group consisting of a cyclic C.sub.3-C.sub.6-alkyl group, a cyclic C.sub.3-C.sub.6-alkylene group, a phenyl group, and a phenylene group, and wherein the cyclic C.sub.3-C.sub.6-alkyl group, the cyclic C.sub.3-C.sub.6-alkylene group, the phenyl group, or the phenylene group is optionally further substituted by 0, 1, 2, or 3 methyl groups; and R.sub.2 and R.sub.3 are hydrogen.

2. The NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole** according to claim 1, wherein R.sub.1 is a linear or branched C.sub.1-C.sub.6-alkyl group, or a cyclic C.sub.3-C.sub.6-alkyl group, wherein the linear or branched C.sub.1-C.sub.6-alkyl group is optionally substituted or interrupted with a substituent selected from the group consisting of a cyclic C.sub.3-C.sub.5-alkyl group, a cyclic C.sub.3-C.sub.5-alkylene group, a phenyl group, or a phenylene group, and wherein the cyclic C.sub.3-C.sub.5-alkyl group, the cyclic C.sub.3-C.sub.5-alkylene group, the phenyl group, or the phenylene group is optionally further substituted by 0, 1, 2, or 3 methyl groups.

3. The NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole** according to claim 1, wherein R.sub.1 is a linear, branched, or cyclic C.sub.4-alkyl group, wherein the linear or branched C.sub.4-alkyl group is optionally substituted or interrupted with a cyclic C.sub.3-alkyl group or a cyclic C.sub.3-alkylene group, and wherein the cyclic C.sub.3-alkyl group or the cyclic C.sub.3-alkylene group is further substituted by 0, 1, 2, or 3 methyl groups.

4. The NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole** according to claim 1, wherein the salt has a pKa value equal to or greater than about 10.

5. The NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole** according to claim 1, wherein the salt has a pKa value equal to or greater than about 10.5.

8. The NHR.sub.1R.sub.2R.sub.3.sup.+ of **omeprazole** according to claim 1, wherein the salt is the tert-butylammonium salt of **omeprazole.**

10. The NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole** according to claim 1, wherein the salt is crystalline.

11. A process for preparation of an NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole** according to any one of claims 1-5, 8, or 10, which comprises the steps of: a) dissolving **omeprazole** in an organic solvent; b) adding an NR.sub.1R.sub.2R.sub.3 compound and precipitating the desired salt; and c) isolating and drying the obtained salt of **omeprazole.**

15. A pharmaceutical composition comprising the NHR.sub.1R.sub.2R.sub.3.sup.+ salt of **omeprazole** according to any one of claims 1-5, 8, or 10 as active ingredient in association with pharmaceutically acceptable excipients and optionally one or more additional therapeutic ingredients.

L3 ANSWER 2 OF 11 USPATFULL on STN

ACCESSION NUMBER:	2002:81059 USPATFULL		
TITLE:	Tablet for instant and prolonged release of one or more active substances		
INVENTOR(S):	Saslawski, Olivier, Haquenau, FRANCE Orlando, Laurence, Decines, FRANCE		
PATENT ASSIGNEE(S):	Merck Patent Gesellschaft, Darmstadt, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6372255	B1	20020416
	WO 9933448		19990708
APPLICATION INFO.:	US 2000-581992		20000621 (9)

	WO 1998-EP8100	19981211
		20000621 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	FR 1997-16402	19971223

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Spear, James M.
LEGAL REPRESENTATIVE: Millen, White, Zelano & Branigan, P.C.
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 766
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A multi-layer tablet for the instant and prolonged release of active substances comprises at least two layers where the first outer layer comprises a mixture of excipients and an active substance, allowing for the immediate release of the active substance within the first layer, and a second layer, arranged in contact with the first layer. The second layer comprises a nonbiodegradable inert porous polymeric matrix in which an active substance is dispersed, allowing for the prolonged release of the active substance within the second layer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD antiulcer agents such as ranitidine, famotidine, nizatidine, cimetidine, **omeprazole**, of the antiulcer prostaglandin type such as misoprostol, sucralfate, aluminium hydroxide;

DETD According to the invention, "ethylammonium" is understood to mean a radical chosen from the ammonioethyl, (C.sub.1-C.sub.4) **alkylammonioethyl**, di (C.sub.1-C.sub.4) alkyl-ammonioethyl and tri(C.sub.1-C.sub.4)**alkylammonioethyl** groups. Preferably, ethylammonium designates a trimethyl-ammonioethyl radical.

L3 ANSWER 3 OF 11 USPATFULL on STN
ACCESSION NUMBER: 2001:178613 USPATFULL
TITLE: Bismuth compounds
INVENTOR(S): Klaveness, Jo, Oslo, Norway
Berg, Arne, Sandvika, Norway
Almen, Torsten, Falsterbo, Sweden
Golman, Klaes, Rungsted Kyst, Denmark
Droege, Michael, Livermore, CA, United States
Yu, Shi-bao, Campbell, CA, United States
PATENT ASSIGNEE(S): Nycomed Imaging AS, Oslo, Norway (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6303101	B1	20011016
APPLICATION INFO.:	US 1999-473100		19991228 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-369694, filed on 6 Aug 1999, now abandoned Continuation of Ser. No. US 1997-875305, filed on 22 Oct 1997, now patented, Pat. No. US 6117412 Continuation of Ser. No. WO 1996-GB183, filed on 26 Jan 1996 Continuation-in-part of Ser. No. US 1995-486225, filed on 7 Jun 1995, now patented, Pat. No. US 5817289

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1995-1560	19950126

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED

10/506,345

PRIMARY EXAMINER: Jones, Dameron L.
LEGAL REPRESENTATIVE: Fish & Richardson P.C.
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 916
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The use in diagnostic imaging, in particular X-ray, MRI, ultrasound and scintigraphy, of contrast agents comprising bismuth clusters and/or organic bismuth compounds, and contrast media containing such bismuth compounds. The bismuth compounds are also useful in therapy, in particular as antimicrobial agents and antiulcer agents. Novel bismuth compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Various bismuth compounds have been suggested in the prior art as X-ray absorbing agents. Other prior art documents focus on the use of metal chelates in diagnostic imaging, mainly in MRI. In addition, bismuth compounds have a long history in therapeutic medicine specially in treatment of gastrointestinal diseases such as ulcers. Although antiulcer agents such as the H.sub.2 -antagonists cimetidine and ranitidine, and more recently proton pump inhibitors such as **omeprazole**, have been developed, there is still medical use of bismuth compounds in ulcer treatment.

SUMM Suitable counter-ions include for example protons, alkali and alkaline earth metal ions, e.g. sodium, calcium and magnesium and zinc, ammonium and organic cations (e.g. organic amine cations, iodinated organic amine cations, cuarternary ammonium, pyridinium, meglumine, **alkylammonium**, polyhydroxy-**alkylammonium**, baser protonated amino acids etc.), transition metal complex cations and organometallic cations.

L3 ANSWER 4 OF 11 USPATFULL on STN
ACCESSION NUMBER: 2000:121056 USPATFULL
TITLE: Non-cluster type bismuth compounds
INVENTOR(S): Klaveness, Jo, Oslo, Norway
Berg, Ame, Sandvika, Norway
Almen, Torsten, Falstorbo, Sweden
Golman, Klaes, Rungsted Kyst, Denmark
Droege, Michael, Livermore, CA, United States
Yu, Shi-bao, Campbell, CA, United States
PATENT ASSIGNEE(S): Nycomed Imaging AS, Norway (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6117412		20000912	
	WO 9622994		19960801	
APPLICATION INFO.:	US 1997-875305		19971022	(8)
	WO 1996-GB183		19960126	
			19971022	PCT 371 date
			19971022	PCT 102(e) date

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-486225, filed on 7 Jun 1995, now patented, Pat. No. US 5817289

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1995-1560	19950126

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Jones, Dameron

LEGAL REPRESENTATIVE: Fish & Richardson P.C.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 954
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of generating an image of a human or non-human animal body which comprises administering to said body a physiologically tolerable contrast enhancing amount of a non-cluster type bismuth compound, and methods of treating gastrointestinal disorders using the same. Diagnostic imaging contrast media comprising non-cluster type bismuth compounds are also disclosed, together with novel covalent non-cluster type bismuth compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM Various bismuth compounds have been suggested in the prior art as X-ray absorbing agents. Other prior art documents focus on the use of metal chelates in diagnostic imaging, mainly in MRI. In addition, bismuth compounds have a long history in therapeutic medicine specially in treatment of gastrointestinal diseases such as ulcers. Although antiulcer agents such as the H.sub.2 -antagonists cimetidine and ranitidine, and more recently proton pump inhibitors such as **omeprazole**, have been developed, there is still medical use of bismuth compounds in ulcer treatment.

SUMM Suitable counter-ions include for example protons, alkali and alkaline earth metal ions, e.g. sodium, calcium and magnesium and zinc, ammonium and organic cations (e.g. organic amine cations, iodinated organic amine cations, quarternary ammonium, pyridinium, meglumine, **alkylammonium**, polyhydroxy-**alkylammonium**, basic protonated amino acids etc.), transition metal complex cations and organometallic cations.

L3 ANSWER 5 OF 11 USPATFULL on STN
ACCESSION NUMBER: 1998:122050 USPATFULL
TITLE: Non-cluster type bismuth compounds
INVENTOR(S): Klaveness, Jo, Oslo, Norway
Berg, Arne, Sandvika, Norway
Almen, Torsten, Falsterbo, Sweden
Golman, Klaes, Rungsted Kyst, Denmark
Droege, Michael, Livermore, CA, United States
Yu, S. B., Campbell, CA, United States
PATENT ASSIGNEE(S): Nycomed Imaging AS, Norway (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5817289		19981006	
APPLICATION INFO.:	US 1995-486225		19950607	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1995-1560	19950126

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Hollinden, Gary E.
ASSISTANT EXAMINER: Jones, Dameron
LEGAL REPRESENTATIVE: Fish & Richardson PC
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 671
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The use in diagnostic imaging, in particular X-ray, MRI, ultrasound and

scintigraphy, of contrast agents comprising bismuth clusters and/or organic bismuth compounds, and contrast media containing such bismuth compounds. The bismuth compounds are also useful in therapy, in particular as antimicrobial agents and antiulcer agents. Novel bismuth compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Various bismuth compounds have been suggested in the prior art as X-ray absorbing agents. Other prior art documents focus on the use of metal chelates in diagnostic imaging, mainly in MRI. In addition, bismuth compounds have a long history in therapeutic medicine specially in treatment of gastrointestinal diseases such as ulcers. Although antiulcer agents such as the H.sub.2 -antagonists cimetidine and ranitidine, and more recently proton pump inhibitors such as **omeprazole**, have been developed, there is still medical use of bismuth compounds in ulcer treatment.

SUMM Suitable counter-ions include for example protons, alkali and alkaline earth metal ions, e.g. sodium, calcium and magnesium and zinc, ammonium and organic cations (e.g. organic amine cations, iodinated organic amine cations, quarternary ammonium, pyridinium, meglumine, **alkylammonium**, polyhydroxy-**alkylammonium**, basic protonated amino acids etc.), transition metal complex cations and organometallic cations.

L3 ANSWER 6 OF 11 USPATFULL on STN

ACCESSION NUMBER:	96:25082 USPATFULL		
TITLE:	Sulfoxide-carboxylate intermediates of **omeprazole** and lansoprazole		
INVENTOR(S):	Slemon, Clarke, 156 Upper Canada Drive, North York, Ontario, Canada M2P 1S8 Macel, Bob, 208 Simonston Boulevard, Thornhill, Ontario, Canada M2H 1Y3		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5502195		19960326
APPLICATION INFO.:	US 1994-345725		19941122 (8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1994-276378, filed on 18 Jul 1994 which is a division of Ser. No. US 1993-145572, filed on 4 Nov 1993, now patented, Pat. No. US 5374730, issued on 20 Dec 1994		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Fan, Jane		
LEGAL REPRESENTATIVE:	Ridout & Maybee		
NUMBER OF CLAIMS:	2		
EXEMPLARY CLAIM:	1		
LINE COUNT:	340		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB **Omeprazole** and lansoprazole, which are chemically pyridine-benzimidazole sulfinyl compounds, are produced from the corresponding acetamide-sulfide compounds by a process of oxidation to form the amide sulfinyl compound, followed by alkaline hydrolysis to the sulfinyl carboxylate or salt, and decarboxylation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Sulfoxide-carboxylate intermediates of **omeprazole** and lansoprazole

AB **Omeprazole** and lansoprazole, which are chemically pyridine-benzimidazole sulfinyl compounds, are produced from the

corresponding acetamide-sulfide compounds by a process of oxidation to form the amide sulfinyl compound, followed by alkaline hydrolysis to the sulfinyl carboxylate or salt, and decarboxylation.

SUMM This invention relates to **omeprazole** and lansoprazole, and more particularly to novel synthetic methods for their preparation.

SUMM **Omeprazole**, which has the chemical structural formula: ##STR1## is a known gastric acid secretion inhibiting agent, and is prescribed clinically for the prevention and treatment of gastrointestinal inflammatory diseases in mammals including man, for example gastritis, gastric ulcer and duodenal ulcer. Lansoprazole, which has the chemical structural formula: ##STR2## has similar pharmaceutical activity and medicinal uses.

SUMM The reported syntheses of **omeprazole** basically involve the synthesis of the corresponding thioether compound, of the formula: ##STR3## and its subsequent oxidation to the sulfinyl or sulfoxy compound, **omeprazole**, by various methods such as reaction with hydrogen peroxide over a vanadium compound catalyst (Canadian Patent 1,263,119 Takeda), reaction with peracids, peresters, ozone, etc. (Canadian patent 1,127,158) . Lansoprazole similarly is produced by oxidation of the thioether compound of formula: ##STR4## There are certain disadvantages associated with these processes, largely derived from the nature of the thioether (or sulfide) compound being oxidized.

SUMM One of these disadvantages derives from the physical nature of the thioether itself. Under ordinary conditions of temperature and pressure, it is an oil, not a crystalline solid. Accordingly, it is very difficult to purify, since it cannot be subjected to precipitation and crystallization procedures to remove impurities from it. This leads to complications in the processes for purifying the resultant **omeprazole.**

SUMM Another disadvantage associated with both **omeprazole** and lansoprazole derives from the discolouration of the final product made by oxidation of the thioethers. A red discolouration of the crude products is commonly experienced, and is very difficult to avoid, using this oxidation process. **Omeprazole** and lansoprazole are inherently unstable molecules in weakly acidic conditions, tending to rearrange to produce annoying highly coloured decomposition impurities.

SUMM It is an object of the present invention to provide a novel process for the preparation of **omeprazole** and lansoprazole, which overcomes or at least reduces one or more of the disadvantages associated with prior art processes.

SUMM According to the present invention, it has been discovered that amide analogues of the thioether compounds A and B, i.e. compounds meeting the general formula: ##STR5## can be readily oxidized to the corresponding sulfinyl compounds. Then the sulfinyl compounds can by hydrolysed in alkaline medium to the corresponding carboxylic acid salts (alkali metal, alkaline earth metal or organic ammonium salts) which can be decarboxylated to **omeprazole** or lansoprazole, as the case may be.

SUMM This process offers a number of significant advantages. Some of these relate to the purity in which the final products can be obtained, and the simplicity of the purification procedures which can be adopted to achieve high purity. For example, the amide compounds which are subjected to the oxidation step are crystalline solids, as opposed to oils, so that they are readily purified to a high degree of purity by relatively simple precipitation, crystallization and washing procedures.

The carboxylates and carboxylic acid salts which are formed in the next synthetic step after oxidation are water soluble, whereas the final products, **omeprazole** and lansoprazole, are not. Accordingly, any unreacted residues of these compounds and many other minor impurities in the final products are simply removable by an aqueous washing procedure.

SUMM When choice (a) for the various radicals is made, the end product is **omeprazole.** When choice (b) is made, the end product is lansoprazole.

DETD The oxidation of the amide of general formula II can be conducted using a wide variety of oxidizing agents, such as those previously proposed for use in oxidizing thioether compounds of formula A in the synthesis of **omeprazole.** These include the use of hydrogen peroxide as oxidizing agent (with or without catalysts). Other oxidizing agents which can be used include peracids, permanganates, tris(trimethyl) peroxide, N-bromo(chloro)succinimide, 1,3-dibromo-5,5-dimethylhydantoin, 2-hydroperoxyhexafluoro-2-propanol, iodosyl benzene, manganese (III) acetylacetonate, oxygen (with or without a catalyst), peroxy monosulfate, ruthenium tetroxide, perborate, periodate, acyl nitrates, t-butylhydroperoxide, dimethyl dioxiranes, hypochlorite, cerium ammonium nitrate, 2-nitrobenzenesulfinyl chloride/potassium superoxide, N-sulfonyloxaziridines, sodium bromite and benzoyl peroxide etc. The oxidation is suitably conducted in an aqueous or polar organic solvent medium, depending upon the choice of oxidizing reagents, and under other conditions such as temperatures and pressures commonly used in organic synthesis when working with the chosen oxidation system. The oxidation process normally leads to the formation of a mixture of the two diastereomers, reflecting the different configuration around the sulphur group. It is unnecessary to separate these isomers.

DETD The sulfinyl-amide compound of formula II is next subjected to hydrolysis, to form the corresponding carboxylic acid salt. The counter-ion may be alkali metal, alkaline-earth metal (involving the benzodiazole ring nitrogen atoms), ammonium, **alkylammonium** or benzylalkylammonium. Surprisingly, as noted above, this can be readily accomplished simply by heating with an aqueous alkali, suitably sodium or potassium hydroxide solution so as to obtain an alkali metal salt of the carboxylic acid, an **alkylammonium** hydroxide to obtain the **alkylammonium** salt or a benzylalkylammonium hydroxide to obtain the benzylalkylammonium salt. Normally one encounters difficulties in achieving hydrolysis of amides of this type, perhaps due to steric hindrance effects or the presence of competitive reactive groups in the molecular structure. This does not appear to happen in the process of the present invention.

DETD The salt form can be isolated and used in the decarboxylation step or it can be converted in situ. The alkali metal, salts, alkaline earth metal salts and organic ammonium salts are solids at ordinary temperatures, so that recovery and purification is relatively easy and straightforward. They are water soluble. Following the recovery of the salt, it can be heated in solution to effect decarboxylation and formation of **omeprazole** or lansoprazole, as the case may be. In a preferred embodiment of the invention, the salt is not isolated but is warmed in situ in a solvent medium in which it is soluble but in which the product, **omeprazole** or lansoprazole, is not. The product as it is formed crystallizes out. These final compounds are insoluble in water. The use of the salt form for decarboxylation purposes, with the attendant avoidance of acidification to acidic pHs, removes further risk of discolouration of the end product as discussed above. It appears that the compounds of general formula III have sufficient internal acidity for the decarboxylation reaction, derived from the proton associated with the imidazole ring system, so that neutral or even weakly alkaline

conditions can be adopted for this reaction, if desired.

DETD The end product **omeprazole** or lansoprazole produced by the process of the present invention is easily and simply purified from the residual, unreacted salt, inorganic byproducts and other minor by-products by a washing procedure. The desired end products are insoluble in water and lower alkanol solvents, whereas the starting materials and byproducts are soluble therein. Consequently, solvent extractions, filtrations and washings are all the steps that are necessary to obtain the end products in highly purified form.

DETD The amide sulfoxide product of Example 1, 2-(5'-methoxy-2'-benzimidazolylsulfinyl)-2-(3,5-dimethyl-4-methoxypyridyl)acetamide sodium salt, was converted to the corresponding acetic acid sodium salt by hydrolysis, and then thermolyzed to give **omeprazole.**

DETD 1.00 g of the amide sulfoxide substrate in 5 mL of 10% sodium hydroxide was heated under nitrogen in an oil bath at 50 degrees. The transformation from amide to carboxylate was monitored by HPLC. The reaction was essentially complete in three hours. The mixture was acidified with carbon dioxide and the intermediate2-(5'-methoxy-2'-benzimidazolylsulfinyl)2-(3,5-dimethyl-4-methoxypyridyl)sodium carboxylate was extracted into 1:1 v/v isopropanol-toluene. The solution was refluxed for 20-30 minutes and the transformation of the carboxylate into **omeprazole** was monitored by HPLC. The organic mixture was evaporated and the organic materials dissolved in warm isopropanol and filtered to remove inorganic residues. The solution was stirred and cooled to give slow crystallization of a cream coloured solid. The solid was filtered and washed with cold isopropanol and with hexanes. Yield--0.37 g.

DETD **Omeprazole** was produced from 2-(5'-methoxy-2'-benzimidazolylsulfinyl)-2-(3,5-dimethyl-4-methoxypyridyl) acetic acid dipotassium salt substrate, as follows:

DETD 1.0g of substrate was dissolved in 1.0 ml water and mixed with 10 ml of a bisulfite solution pH 4.8, which was prepared by combining 5.0gm of sodium metabisulfite with 75 ml water and 25 ml of methanol. The pH of the total reaction mixture was 7.2. Gradually at room temperature with stirring, 35 drops of glacial acetic acid were added from a disposable pipette, bringing the pH to 4.8. Vigorous gas evolution was observed and the solution became cloudy, then oily. 2.0 ml of methanol was added and the mixture seeded with **omeprazole**; solid began to precipitate. The reaction was allowed to proceed for 30 minutes. The solid was filtered, washed with water, and then some acetone. Drying gave 0.45 g of off-white **omeprazole** free of any substantial impurities.

DETD A 300 ml three-necked flask equipped with a reflux condenser, a thermometer, a magnetic stirrer and a nitrogen bubbler was flushed with nitrogen, and the inert atmosphere maintained throughout the reaction. To 19.4 g of 2-[4-methoxy-3,5-dimethyl-2-pyridyl]-2-[2-(5-methoxy-benzimidazolyl)]acetamide (the sulfoxy-amide) was added 80.0 ml of 40% aqueous benzyl trimethylammonium hydroxide (Triton B) and the clear yellow solution was heated at 48-52 degrees C. for 12 hours. The solution was cooled to 40 degrees and 20 ml ethyl acetate was added over 30 minutes. The solution was heated to 48-52 degrees for an additional 8 hours. The solution was cooled to 20-25 degrees by adding 80 ml cold water. The solution was seeded with **omeprazole** and a steady stream of carbon dioxide passed lowering the pH steadily to 9.6-9.1. The product soon started to crystallize as the pH declined. The slurry was cooled to 0-5 degrees for two hours while maintaining the atmosphere of carbon dioxide. During this time, the pH dropped further to 7.0-7.5 where it remained constant. The solid was filtered on a Buchner funnel, washed with 3+25 ml of water and resuspended in 100 ml of water. After stirring for 15 minutes the solid was again filtered and washed with 25 ml of water. The reaction product was purified by slurrying in 60 ml of methanol and 30 ml of concentrated ammonium hydroxide. The

slurry was charcoal filtered and carbon dioxide was passed into the clear solution until the pH was brought down to 10-10.2. The solution was seeded and further carbon dioxide added to bring the pH down to 7.3-7.5. The product was isolated by vacuum filtration on a Buchner funnel. The solid was washed, then re-slurried in water and re-filtered. The wet product was dried at 40-50 degrees to constant weight to give 11.9 g of pure **omeprazole.**

L3 ANSWER 7 OF 11 USPATFULL on STN

ACCESSION NUMBER:	92:46879 USPATFULL		
TITLE:	Swelling modulated polymeric drug delivery device		
INVENTOR(S):	McClelland, Gregory A., Lawrence, KS, United States Zentner, Gaylen M., Lawrence, KS, United States		
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5120548		19920609
APPLICATION INFO.:	US 1989-433056		19891107 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Page, Thurman K.		
ASSISTANT EXAMINER:	Kishore, G. S.		
LEGAL REPRESENTATIVE:	Perrella, Donald J., Winokur, Melvin, DiPrima, Joseph F.		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)		
LINE COUNT:	558		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A controlled release drug delivery device, comprised of swellable polymers, whose degree of swelling in an environment of use is controlled by swelling modulators blended within the polymers, is disclosed. The swelling modulators can include buffers, osmagents, surfactants or combinations thereof surrounded by a microporous coating or interspersed within individual matrices. The combination of controlled release swelling modulators with swellable polymers may be applied to regulate patterns of beneficial agent (typically a drug) release.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Surfactants are comprised of those compounds that decrease surface and interfacial tension and serve to enhance and facilitate wetting. As such they serve to promote interactions between water and swellable polymers and hence modulate the swelling properties of those polymers. Generally, the surfactants are amphipathic molecules comprised of a hydrophobic part and a hydrophilic part. The surfactants useful in the present invention can be anionic, cationic, nonionic or amphoteric. The anionic surfactants include sulfated, sulfonated, or carboxylated esters, amide, alcohols, ethers, aromatic hydrocarbons, aliphatic hydrocarbons, acylated amino acids and peptides. Metal alkyl phosphates are another class of anionic surfactant. Typically, cationic surfactants are primary, secondary, tertiary or quarternary **alkylammonium** salts, acylated polyamines, and salts of heterocyclic amines. Nonionic surfactants are typically esters and ethers of polyoxyalkylene glycols, polyhydric alcohols, or phenols. Poloxamers and poloxamines are included as nonionic surfactants. Surfactants are discussed in Surfactant Systems, Their Chemistry, Pharmacy, and Biology, D. Attwood and A. T. Florence, Chapman and Hall Pub. Co., 1983.

DETD Beneficial agents, including inorganic and organic compounds useful in

the present invention includes substances that produce localized or systemic effects in humans or animals resulting in desirable functions and responses. Examples include but are not limited to amitripytline, haloperidol, diazepam, cyclobenzaprine, carbidopa, levodopa, acetaminophen, isoproterenol, chlorpheniramine, digoxin, timolol, nifedipine, diltiazem, methyldopa, enalapril, lysinopril, felodipine, hydrochlorothiazide, simvastatin, lovastatin, ethinyl estradiol, dexamethasone, indomethacin, sulindac, diflunisal, ranitidine, famotidine, **omeprazole**, norfloxacin, ivermectin, pravistatin. Typical beneficial agent loadings range from about 0.05 nanograms to 5 grams or more.

L3 ANSWER 8 OF 11 USPATFULL on STN
ACCESSION NUMBER: 90:85444 USPATFULL
TITLE: Controlled porosity osmotic pump
INVENTOR(S): Zentner, Gaylen M., Lawrence, KS, United States
Rork, Gerald S., Lawrence, KS, United States
Himmelstein, Kenneth J., Irvine, CA, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4968507		19901106
APPLICATION INFO.:	US 1987-73781		19870715 (7)

DISCLAIMER DATE: 20060725
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1986-850576, filed on 11 Apr 1986, now abandoned which is a continuation of Ser. No. US 1985-689540, filed on 7 Jan 1985, now abandoned which is a continuation-in-part of Ser. No. US 1984-622808, filed on 20 Jun 1984, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Griffin, Ronald W.
LEGAL REPRESENTATIVE: McGough, Kevin J., DiPrima, Joseph F., Sudol, Jr., Michael C.
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 1301
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The instant invention is directed to an osmotic pump comprising:

(A) at least one active agent surrounded by

(B) a rate controlling water insoluble wall, having a fluid permeability of 6.96+10.sup.-18 to 6.96+10.sup.-14 cm.sup.3 sec/g and a reflection coefficient of less than 1, prepared from:

(i) a polymer permeable to water but impermeable to solute and

(ii) 0.1 to 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout said wall.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Surfactants useful for the present purpose are those surfactants, when added to a wall forming material and other materials, aid in producing an integral composite that is useful for making the operative wall of a device. The surfactants act by regulating the surface energy of materials to improve their blending into the composite. This latter material is used for manufacturing devices that maintain their integrity

in the environment of use during the agent release period. Generally, the surfactants are amphipathic molecules comprised of a hydrophobic part and a hydrophilic part. The surfactants can be anionic, cationic, nonionic or amphoteric, and they include anionics such as sulfated esters, amides, alcohols, ethers and carboxylic acids; sulfonated aromatic hydrocarbons, aliphatic hydrocarbons, esters and ethers; acylated amino acids and peptides; and metal alkyl phosphates; cationic surfactants such as primary, secondary, tertiary and quaternary **alkylammonium** salts; acylated polyamines; and salts of heterocyclic amines, arylammonium surfactants such as esters of polyhydric alcohols; alkoxylated amines; polyoxyalkylene; esters and ethers of polyoxyalkylene glycols; alkanolamine fatty acid condensates; tertiary acetylamic glycols; and dialkyl polyoxyalkylene phosphates; and ampholytics such as betamines; and amino acids.

DETD Typical surfactants include polyoxyethylenated glycerol ricinoleate; polyoxyethylenated castor oil having from 9 to 52 moles of ethylene oxide; glycerol mannitan laurate, and glycerol (sorbitan oleates, stearates or laurates); polyoxyethylenated sorbitan laurate, palmitate, stearate, oleate or hexaolate having from 5 to 20 moles of ethylene oxide; mono-, di- and poly-ethylene glycol stearates, laurates, oleates, myristates, behenates or ricinoleates; propylene glycol carboxylic acid esters; sorbitan laurate, palmitate, oleate, and stearate; polyoxyethylenated octyl, nonyl, decyl, and dodecylphenols having 1 to 100 moles of ethylene oxide; polyoxyethylenated nonyl, lauryl, decyl, cetyl, oleyl and stearyl alcohols having from 3 to 50 moles of ethylene oxide; polyoxypropylene glycols having from 3 to 300 moles of ethylene oxide; sodium salt of sulfated propyl oleate; sodium di-(heptyl)-sulfosuccinate; potassium xylenesulfonate; 1:1 myristic acid diethanolamide; N-coco-β-aminopropionic acid; bis-(2-hydroxyethyl)-tallowamine oxide; (diisobutyl-phenoxyethoxyethyl)dimethylbenzylammonium halide; N,N'-polyoxypropylenated ethylenediamine having a molecular weight from 500 to 3000; tetra-**alkylammonium** salts with up to 26 carbon atoms in the cation; sodium or potassium salt of polypeptide cocoanut, oleic or undecylenic acid condensate; metal salts of N-acylated short chain aminosulfonic acids, soybean phosphatides; and sulfobetaine.

DETD Additional preferred drugs include drugs which affect the respiratory tract such as budesonide, enprofylline, tranilast, albuterol, theophylline, aminophylline, brompheniramine, chlorpheniramine, promethazine, diphenhydramine, azatadine, cyproheptadine, terbutaline, metaproterenol, and isoproterenol; drugs which are antidepressants such as amiflamine, alaproclate, doxepin, trazedone, maprotiline, zimelidine, fluvoxamine; antipsychotic drugs such as haloperidol, thioridazine, trifluoperazine, MK-0212, and remoxipride; sedative hypnotic and antianxiety drugs such as triazolam, temazepam, chlorazepate, alprazolam, diazepam, flurazepam, lorazepam, oxazepam, hydroxyzine, prazepam, meprobamate, butalbital, and chlorzoxazone; antiparkinson drugs such as benztropine and L-647,339; hormonal and steroidal drugs such as conjugated estrogens, diethylstilbesterol, hydroxy progesterone, medroxy progestrone, norethindrone, betamethasone, methylprednisolone, prednisone, thyroid hormone, levothyroxine and MK-0621; antihypertensive and cardiovascular drugs such as isosorbide dinitrate, digoxin, nadolol, disopyramide, nifedipine, quinidine, lidocaine, diltiazam, verapamil, prazosin, captopril, enalapril, lisinopril, metyrosine, felodipine, tocainide, mexiletine, mecamylamine, and metyrosine; diuretic drugs such as spironolactone, chlorthalidone, metolazone, triamterene, methyclothiazide, and indacrinone; antiinflammatory drugs such as ibuprofen, phenylbutazone, tolmetin, piroxicam, melclofenamate, auranofin, flurbiprofen and penicillamine; analgesic drugs such as acetaminophen, oxycodone, hydrocodone, and propoxyphene; antiinfective drugs such as cefoxitin, cefazolin, cefotaxime, cephalexin, nicarbazin, amprolium, ampicillin, amoxicillin, cefaclor, erythromycin,

nitrofurantoin, minocyline, doxycycline, cefadroxil, miconazole clotrimazole, phenazopyridine, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, imipenem, arprinocid, and foscarnet; gastrointestinal drugs such as bethanechol, clidinium, dicyclomine, meclizine, prochlorperizine, trimethobenzamide, loperamide, ranitidine, diphenoxylate, famotidine, metoclopramide and **omeprazole**; anticoagulant drugs such as warfarin, phenindione, and anisindione; and other drugs such as trientine, cambendazole, ronidazole, rafoxinide, dactinomycin, asparaginase, nalorphine, rifamycin, carbamezepine, metaraminol bitartrate, allopurinol, probenecid, diethylpropion, dihydrogenated ergot alkaloids, nystatin, pentazocine, phenylpropanolamine, phenylephrine, pseudoephedrine, trimethoprim and mevinolin.

L3 ANSWER 9 OF 11 USPATFULL on STN

ACCESSION NUMBER:	89:60695 USPATFULL
TITLE:	Multiparticulate controlled porosity osmotic
INVENTOR(S):	Zentner, Gaylen M., Lawrence, KS, United States Himmelstein, Kenneth J., Irvine, CA, United States Rork, Gerald S., Lawrence, KS, United States
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4851228		19890725
APPLICATION INFO.:	US 1987-73596		19870715 (7)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1986-850576, filed on 11 Apr 1986, now abandoned which is a continuation of Ser. No. US 1985-689540, filed on 7 Jan 1985, now abandoned which is a continuation of Ser. No. US 1984-622808, filed on 20 Jun 1984, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Page, Thurman K.		
ASSISTANT EXAMINER:	Horne, Leon R.		
LEGAL REPRESENTATIVE:	DiPrima, Joseph F., Sudol, Michael C., McGough, Kevin J.		
NUMBER OF CLAIMS:	20		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	20 Drawing Figure(s); 20 Drawing Page(s)		
LINE COUNT:	1360		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The instant invention is directed to a multiparticulate osmotic pump, for the controlled release of a pharmaceutically active agent to an environment of use, said pump comprising:

(I) a carrier medium which does not maintain its integrity in the environment of use;

(II) a multiple of tiny osmotic pump elements each consisting essentially of:

(A) a core comprises at least one pharmacologically active agent soluble in an external fluid, or a mixture of an agent having a limited solubility in the external fluid with an osmotically effective solute that is soluble in the fluid, which exhibit an osmotic pressure gradient across the wall against the external fluid surrounded by

(B) a rate controlling water insoluble wall, having a fluid permeability of 6.96+10.sup.-18 to 6.96+10.sup.14 cm.sup.3 sec/g and a reflection coefficient of less than 0.5, prepared from:

(i) a polymer permeable to water but impermeable to solute and

(ii) 0.1 to 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout said wall.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Surfactants useful for the present purpose are those surfactants, when added to a wall forming material and otehr materials, aid in producing an integral composite that is useful for making the operative wall of a device. The surfactants act by regulating the surface energy of materials to improve their blending into the composite. This latter material is used for manufacturing devices that maintain their integrity in the environment of use during the agent release period. Generally, the surfactants are amphipathic molecules comprised of a hydrophobic part and a hydrophilic part. The surfactants can be anionic, cationic, nonionic or amphoteric, and they include anionics such as sulfated esters, amides, alcohols, ethers and carboxylic acids; sulfonated aromatic hydrocarbons, aliphatic hydrocarbons, esters and ethers; acylated amino acids and peptides; and metal alkyl phosphates; cationic surfactants such as primary, secondary, tertiary and quaternary **alkylammonium** salts; acylated polyamines; and salts of heterocyclic amines, arylammonium surfactants such as esters of polyhydric alcohols; alkoxylated amines; polyoxyalkylene; esters and ethers of polyoxyalkylene glycols; alkanolamine fatty acid condensates; tertiary acetylamic glycols; and dialkyl polyoxyalkylene phosphates; and ampholytics such as betamines; and amino acids.

DETD Typical surfactants include polyoxyethylenated glycerol ricinoleate; polyoxyethylenated castor oil having from 9 to 52 moles of ethylene oxide; glycerol mannitan laurate, and glycerol (sorbitan oleates, stearates or laurates); polyoxyethylenated sorbitan laurate, palmitate, stearate, oleate or hexaolate having from 5 to 20 moles of ethylene oxide; mono-, di- and poly-ethylene glycol stearates, laurates, oleates, myristates, behenates or ricinoleates; propylene glycol carboxylic acid esters; sorbitan laurate, palmitate, oleate, and stearate; polyoxyethylenated octyl, nonyl, decyl, and dodecylphenols having 1 to 100 moles of ethylene oxide; polyoxyethylenated nonyl, lauryl, decyl, cetyl, oleyl and stearyl alcohols having from 3 to 50 moles of ethylene oxide; polyoxypropylene glycols having from 3 to 300 moles of ethylene oxide; sodium salt of sulfated propyl oleate; sodium di-(heptyl)sulfosuccinate; potassium xylenesulfonate; 1:1 myristic acid diethanolamide; N-coco-β-aminopropionic acid; bis-(2-hydroxyethyl)-tallowamine oxide; (diisobutyl-phenoxyethoxyethyl)dimethylbenzylammonium halide; N,N'-polyoxypropylenated ethylenediamine having a molecular weight from 500 to 3000; tetra-**alkylammonium** salts with up to 26 carbon atoms in the cation; sodium or potassium salt of polypeptide cocoanut, oleic or undecylenic acid condensate; metal salts of N-acylated short chain aminosulfonic acids, soybean phosphatides; and sulfobetaine.

DETD Additional preferred drugs include drugs which affect the respiratory tract such as budesonide, enprofylline, tranilast, albuterol, theophylline, amoniphylline, brompheniramine, chlorpheniramine, promethazine, diphenhydramine, azatadine, cyproheptadine, terbutaline, metaproterenol, and isoproterenol; drugs which are antidepressants such as amiflamine, alaproclate, doxepin, trazedone, maprotiline, zimelidine, fluvoxamine; antipsychotic drugs such as haloperidol, thioridazine, trifluoperazine, MK-0212, and remoxipride; sedative hypnotic and antianxiety drugs such as triazolam, temazepam, chlorazeptate, alprazolam, diazepam, fluorazepam, lorazepam, oxazepam, hydroxyzine, prazepam, meprobamate, butalbital, and chlorzoxazone; antiparkinson drugs such as benztropine and L-647,339; hormonal and steroidal drugs

such as conjugated estrogens, diethylstilbesterol, hydroxy progesterone, medroxy progestrone, norethindrone, betamethasone, methylprednisolone, prednisone, thyroid hormone, levothyroxine and MK-0621; antihypertensive and cardiovascular drugs such as isosorbide dinitrate, digoxin, nadolol, disopyramide, nifedipine, quinidine, lidocaine, diltiazam, verapamil, prazosin, captopril, enalapril, lisinopril, metyrosine, felodipine, tocainide, mexiletine, mecamylamine, and metyrosine; diuretic drugs such as spironolactone, chlorthalidone, metolazone, triamterene, methyclothiazide, and indacrinone; antiinflammatory drugs such as ibuprofen, phenylbutazone, tolmetin, piroxicam, melclofenamate, auranofin, flurbiprofen and penicillamine; analgesic drugs such as acetaminophen, oxycodone, hydrocodone, and propoxyphene; antiinfective drugs such as cefoxitin, cefazolin, cefotaxime, cephalexin, nicarbazin, amprolium, ampicillin, amoxicillin, cefaclor, erythromycin, nitrofurantoin, minocyline, doxycycline, cefadroxil, miconazole clotrimazole, phenazopyridine, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, imipenem, arprinocid, and foscarnet; gastrointestinal drugs such as bethanechol, clidinium, dicyclomine, meclizine, prochlorperizine, trimethobenzamide, loperamide, ranitidine, diphenoxylate, famotidine, metoclopramide and **omeprazole**; anticoagulant drugs such as warfarin, phenindione, and anisindione; and other drugs such as trientine, cambendazole, ronidazole, rafoxinide, dactinomycin, asparaginase, nalorphine, rifamycin, carbamezepine, metaraminol bitartrate, allopurinol, probenecid, diethylpropion, dihydrogenated ergot alkaloids, nystatin, pentazocine, phenylpropanolamine, phenylephrine, pseudoephedrine, trimethoprim and mevinolin.

L3 ANSWER 10 OF 11 USPATFULL on STN

ACCESSION NUMBER:	89:21022 USPATFULL		
TITLE:	Device for the controlled release of drugs with Donnan-like modulation by charged insoluble resins		
INVENTOR(S):	Zentner, Gaylen M., Lawrence, KS, United States		
PATENT ASSIGNEE(S):	Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4814183		19890321
APPLICATION INFO.:	US 1987-91571		19870831 (7)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Dixon, Jr., William R.		
ASSISTANT EXAMINER:	Griffis, Andrew		
LEGAL REPRESENTATIVE:	DiPrima, Joseph F., Sudol, Michael C.		
NUMBER OF CLAIMS:	20		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	4 Drawing Figure(s); 4 Drawing Page(s)		
LINE COUNT:	1024		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The instant invention is directed to a drug delivery device for the controlled release of beneficial agents and drugs into an environment of use comprising:

(A) a core composition comprising

(a) a water insoluble, non-diffusible charged resin entity, and

(b) a diffusible, water soluble ionizable therapeutically active ingredient carrying the same charge as said resin entity; and

(B) a substantially imperforate water-insoluble wall surrounding said

core composition, prepared from a semipermeable material substantially impermeable to the core composition and permeable to the passage of an external fluid in the environment of use, with said wall having a hole(s) for release of the therapeutic agent through the water insoluble wall.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Additional preferred drugs include budesonide, enprofylline, tranilast, albuterol, theophylline, aminophylline, brompheniramine, chlorpheniramine, promethazine, diphenhydramine, azatadine, cyproheptadine, terbutaline, metaproternol, and isoproterenol; drugs which are antidepresessants such as doxepin, trazodone; antipsychotic drugs such as haloperidol, thioridazine, trifluoperazine; sedative hypnotic and antianxiety drugs such as triazolam, temazepam, chlorazepate, alprazolam, diazepam, flurazepam, lorazepam, oxazepam, hydroxyzine, prazepam, meprobamate, butalbital, and chlorzoxazone; antiparkinson drugs such as benztropine and noxazinol; hormonal and steroidal drugs such as conjugated estrogens, diethylstilbesterol, hydroxy progesterone, medroxy proqestrone, norethindrone, betamethasone, methylprednisolone, prednisone, thyroid hormone, and levothyroxine; antihypertensive and cardiovascular drugs such as isosorbide dinitrate, digoxin, nadolol, disopyramide, nifedipine, quinidine, lidocaine, diltiazem hydrochloride, verapamil, prazosin, captopril, enalapril, lisinopril, metyrosine, felodipine, tocainide, mexiletine, mecamylamine, and metyrosine; diuretic drugs such as spironolactone, chlorthalidone, metolazone, triamterene, methyclothiazide, and indacrinone; antiinflammatory drugs such as ibuprofen, ibuprofen lysinate, phenylbutazone, tolmetin, piroxicam, melclofenamate, auranofin, flurbiprofen and penicillamine; analgesic drugs such as acetaminophen, oxycodone, hydrocodone, and propoxyphene; antiinfective drugs such as cefoxitin, cefazolin, cefotaxime, cephalexin, nicarbazin, amprolium, ampicillin, amoxicillin, cefaclor, erythromycin, nitrofurantoin, minocycline, doxycycline, cefadroxil, miconazole, clotrimazole, phenazopyridine, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, imipenem, arprinocid, and foscarnet; gastrointestinal drugs such as bethanechol, clidinium, dicyclomine, meclizine, prochlorperizine, trimethobenzamide, loperamide, ranitidine, diphenoxylate, famotidine, metoclopramide and **omeprazole**; anticoagulant drugs such as warfarin, phenindione, and anisindione; and other drugs such as trientine, cambendazole, ronidazole, rafoxinide, dactinomycin, asparaginase, nalorphine, rifamycin, carbamezepine, metaraminol bitartrate, allopurinol, probenecid, diethylpropion, dihydrogenated ergot alkaloids, nystatin, pentazocine, phenylpropanolamine, phenylephrine, pseudoephedrine, trimethoprim, lovastatin, eptastatin, simvastatin, ivermectin, and milbemycin.

DETD Surfactants useful for the present wall forming purpose are those surfactants, when added to a wall forming material and other materials, aid in producing an integral composite that is useful for making the operative wall of a device. The surfactants act by regulating the surface energy of materials to improve their blending into the composite. The composite material is used for manufacturing devices that maintain their integrity in the environment of use during the agent release period. Generally, the surfactants are amphipathic molecules comprised of a hydrophobic part and a hydrophilic part. The surfactants can be anionic, cationic, nonionic or amphoteric. The anionic surfactants include sulfated, sulfonated, or carboxylated esters, amides, alcohols, ethers, aromatic hydrocarbons, aliphatic hydrocarbons, acylated amino acids and peptides. Metal alkyl phosphates are another class of anionic surfactant. Typically, cationic surfactants are primary, secondary, tertiary or quaternary **alkylammonium** salts, acylated polyamines, and salts of heterocyclic amines. Nonionic surfactants are typically esters and ethers of polyoxyalkylene glycols,

polyhydric alcohols, or phenols. Poloxamers are included as nonionic surfactants. Ampholytic molecules such as betaine are also surfactants. Surfactants are discussed in Surfactant Systems, Their Chemistry, Pharmacy, and Biology, D. Attwood and A. T. Florence, Chapman and Hall Pub. Co., 1983, pgs 1-8.

L3 ANSWER 11 OF 11 USPATFULL on STN
ACCESSION NUMBER: 89:1124 USPATFULL
TITLE: Device for pH independent release of drugs through the Donnan-like influence of charged insoluble resins
INVENTOR(S): Zentner, Gaylen M., Lawrence, KS, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4795644		19890103	
APPLICATION INFO.:	US 1987-81090		19870803	(7)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Horne, L. R.
LEGAL REPRESENTATIVE: DiPrima, Joseph F., Sudol, Michael C.
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 983
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A device is disclosed for the controlled delivery of a beneficial agent. The agent is delivered to the environment surrounding the device at a substantially constant rate for a specified period with a reduced dependence on the environmental pH. The device is comprised of a core compartment containing (1) a charged, water insoluble, non-diffusible component and (2) at least one diffusable water soluble ionizable beneficial agent. The core is surrounded by a water insoluble wall containing leachable pore forming additive(s) dispersed throughout said wall, with said wall impermeable to core components (1) and permeable to beneficial agent(s) (2). In operation the insoluble charged component (often polymeric resins) and water soluble ionizable beneficial agent have the same electro-static charge and do not form an ion exchange complex. Rather, a Donnan influenced mass transport phenomena of the beneficial agent is effected through the pores in the device, actuated by water from the environment, with migration of the freely mobile diffusible species (beneficial agent) away from the non-mobile species (charged entity). This effects the release of the beneficial agent through the wall at a controlled rate with reduced pH dependency.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Additional preferred drugs include budesonide, enprofylline, tranilast, albuterol, theophylline, aminophylline, brompheniramine, chlorpheniramine, promethazine, diphenhydramine, azatadine, cyproheptadine, terbutaline, metaproterenol, and isoproterenol; drugs which are antidepressants such as doxepin, trazodone; antipsychotic drugs such as haloperidol, thioridazine, trifluoperazine; sedative hypnotic and antianxiety drugs such as triazolam, temazepam, chlorazepate, alprazolam, diazepam, flurazepam, lorazepam, oxazepam, hydroxyzine, prazepam, meprobamate, butalbital, and chlorzoxazone; antiparkinson drugs such as benztropine and noxazinol; hormonal and steroidal drugs such as conjugated estrogens, diethylstilbesterol, hydroxy progesterone, medroxy progestrone, norethindrone, betamethasone, methylprednisolone, prenisone, thyroid hormone, and levothyroxine; antihypertensive and cardiovascular drugs such as isosorbide dinitrate,

digoxin, nadolol, disopyramide, nifedipine, quinidine, lidocaine, diltiazem hydrochloride, verapamil, prazosin, captopril, enalapril, lisinopril, metyrosine, felodipine, tocainide, mexiletine, mecamylamine, and metyrosine; diuretic drugs such as spironolactone, chlorthalidone, metolazone, triamterene, methyclothiazide, and indacrinone; antiinflammatory drugs such as ibuprofen, ibuprofen lysinate, phenylbutazone, tolmetin, piroxicam, melclofenamate, auranofin, flurbiprofen and penicillamine; analgesic drugs such as acetaminophen, oxycodone, hydrocodone, and propoxyphene; antiinfective drugs such as cefoxitin, cefazolin, cefotaxime, cephalexin, nicarbazin, amprolium, ampicillin, amoxicillin, cefaclor, erythromycin, nitrofurantoin, minocycline, doxycycline, cefadroxil, miconazole, clotrimazole, phenazopyridine, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, imipenem, arprinocid, and foscarnet; gastrointestinal drugs such as bethanechol, clidinium, dicyclomine, meclizine, proclorperizine, trimethobenzamide, loperamide, ranitidine, diphenoxylate, famotidine, metoclopramide and **omeprazole**; anticoagulant drugs such as warfarin, phenindione, and anisindione; and other drugs such as trientine, cambendazole, ronidazole, rafoxinide, dactinomycin, asparaginase, nalorphine, rifamycin, carbamezepine, metaraminol bitartrate, allopurinol, probenecid, diethylpropion, dihydrogenated ergot alkaloids, nystatin, pentazocine, phenylpropanolamine, phenylephrine, pseudoephedrine, trimethoprim, lovastatin, eptastatin, simvastatin, and ivermectin.

DETD Surfactants useful for the present purpose are those surfactants, when added to a wall forming material and other materials, aid in producing an integral composite that is useful for making the operative wall of a device. The surfactants act by regulating the surface energy of materials to improve their blending into the composite. The composite material is used for manufacturing devices that maintain their integrity in the environment of use during the agent release period. Generally, the surfactants are amphipathic molecules comprised of a hydrophobic part and a hydrophilic part. The surfactants can be anionic, cationic, nonionic or amphoteric. The anionic surfactants include sulfated, sulfonated, or carboxylated esters, amides, alcohols, ethers, aromatic hydrocarbons, aliphatic hydrocarbons, acylated amino acids and peptides. Metal alkyl phosphates are another class of anionic surfactant. Typically, cationic surfactants are primary, secondary, tertiary or quaternary **alkylammonium** salts, acylated polyamines, and salts of heterocyclic amines. Nonionic surfactants are typically esters and ethers of polyoxyalkylene glycols, polyhydric alcohols, or phenols. Poloxamers are included as nonionic surfactants. Ampholytic molecules such as betaine are also surfactants. Surfactants are discussed in Surfactant Systems, Their Chemistry, Pharmacy, and Biology, D. Attwood and A. T. Florence, Chapman and Hall Pub. Co., 1983, pgs 1-8.

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L1   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:719472  CAPLUS
DOCUMENT NUMBER:          139:235513
TITLE:                    Alkylammonium salts of omeprazole and
                          esomeprazole
INVENTOR(S):              Dahlstroem, Mikael
PATENT ASSIGNEE(S):       Astrazeneca AB, Swed.
SOURCE:                   PCT Int. Appl., 27 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2003074514         A1    20030912    WO 2003-SE378           20030304
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2474246            AA    20030912    CA 2003-2474246         20030304
     AU 2003208686         A1    20030916    AU 2003-208686          20030304
     EP 1487818            A1    20041222    EP 2003-707279          20030304
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

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US 2005182099	A1	20050818	US 2003-506345		20030304
PRIORITY APPLN. INFO.:			US 2002-362187P	P	20020305
			WO 2003-SE378	W	20030304

AB The present invention relates to salts of omeprazole and its (S)-enantiomer, **esomeprazole**. More specifically, the present invention relates to **alkylammonium** salt of the compds., formed by a reaction of omeprazole and **esomeprazole**, resp., and an alkylamine. A process for preparing crystalline salts, a pharmaceutical preparation and a method for treatment of gastric acid related disorders by administering the compound of the invention are also described.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Alkylammonium** salts of omeprazole and **esomeprazole**

AB The present invention relates to salts of omeprazole and its (S)-enantiomer, **esomeprazole**. More specifically, the present invention relates to **alkylammonium** salt of the compds., formed by a reaction of omeprazole and **esomeprazole**, resp., and an alkylamine. A process for preparing crystalline salts, a pharmaceutical preparation and a method for treatment of gastric acid related disorders by administering the compound of the invention are also described.

ST omeprazole **esomeprazole alkylammonium** salt prepn
gastric acid disorder

IT Drug delivery systems
(preparation of omeprazole and **esomeprazole alkylammonium** salts for treatment of gastric acid related disorders)

IT Amines, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of omeprazole and **esomeprazole alkylammonium** salts for treatment of gastric acid related disorders)

IT Gastric acid
(secretion, disorders related to; preparation of omeprazole and **esomeprazole alkylammonium** salts for treatment of gastric acid related disorders)

IT 595555-77-4P 595555-78-5P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of omeprazole and **esomeprazole alkylammonium** salts for treatment of gastric acid related disorders)

IT 75-64-9, tert-Butylamine, reactions 73590-58-6, Omeprazole 161796-78-7, **Esomeprazole** sodium
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of omeprazole and **esomeprazole alkylammonium** salts for treatment of gastric acid related disorders)

IT 119141-88-7P, **Esomeprazole**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of omeprazole and **esomeprazole alkylammonium** salts for treatment of gastric acid related disorders)

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